UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/768,020 | 01/23/2001 | Ralph J. Greenspan | P-N1 4577 | 9299 |

41552 7590 06/28/2007

MCDERMOTT, WILL & EMERY
4370 LA JOLLA VILLAGE DRIVE, SUITE 700
SAN DIEGO, CA 92122

| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/28/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/768,020 | GREENSPAN ET AL. | |
| | Examiner | Art Unit | |
| | Quang Nguyen, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30 and 32-36* is/are pending in the application.

4a) Of the above claim(s) *1-21,30 and 32-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

***This application has been transferred to Examiner Quang Nguyen, Ph.D. in GAU 1633.***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/22/07 has been entered.

Claims 1-30 and 32-36 are pending in the present application.

Claims 1-21, 30 and 32-36 were withdrawn previously because they are directed to non-elected inventions.

Accordingly, claims 22-29 are examined on the merits herein.

***Claim Objections***

Claim 22 is objected to because the phrase "test progeny are produced" is grammatically incorrect.

Claims 24-26 are objected to because the abbreviations for terms such as "Appl", "Psn", "har 38", "dCrebA", "dCrebB", "shi", "N", "Su(H)1, "D1", "mam" and "bib" should be spelled out in full at the first occurrence of these terms. Appropriate correction is required.

***Written Description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a modified rejection.***

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of **identifying a therapeutic agent for treating Alzheimer's disease**, comprising the steps of: (a) performing mating between **any first parent strain from any transgenic or non-transgenic organism** (e.g., any invertebrate as well as any vertebrate, including any mammal) carrying **any mutation in any Alzheimer's disease gene** and **a second parent strain from any transgenic or non-transgenic organism containing any genetic variation**, whereby

a test progeny is produced and **it has any altered phenotype relative to at least one sibling control**; (b) administering an agent to at least the first parent strain, the second parent strain or the test progeny; and (c) assaying the test progeny for a modification of the altered phenotype that produces a phenotype with more similarity to a wild type phenotype.

Apart from disclosing a method of mapping genes acting in the same network as the *Drosophila* amyloid protein precursor-like gene (*Appl*) by crossing male *Drosophila* bearing a chromosome that lacks the *Appl* gene ($Appl^d$) with a series of *Drosophila* FM7 virgin females bearing individual deficiencies of the X chromosome "Df(1)s", the instant specification fails to teach and/or describe fully the **essential characteristics and/or elements** possessed by a representative number of species for a broad genus of a first parent strain (any invertebrate as well as any vertebrate) and/or a second parent strain (any invertebrate as well as any vertebrate) and/or **a test progeny having an altered phenotype relative to at least one sibling control and is relevant to the Alzheimer's disease**, such that **the modification of the altered phenotype in the test progeny to a wild type phenotype by an agent would indicate that the agent is a therapeutic agent for treating Alzheimer's disease**. While the $Appl^d$ *Drosophila* parent strain exhibits **a phenotype of defective phototaxis**, and that test progenies resulting from crossings of this $Appl^d$ *Drosophila* parent strain with a series of *Drosophila* females bearing individual deficiencies of the X chromosome display **a non-specific phenotype of either increased or decreased viability** with respect to a sibling control, none of these phenotypes has anything to do specifically to the hall-mark

features of the Alzheimer's disease, let alone a broad genus of an altered phenotype and a modification of said phenotype by an agent is an indication that the agent is a therapeutic agent for treating Alzheimer's disease.

At the effective filing date of the present application, Alzheimer's disease is a neurodegenerative disorder with a progressive dementia **characterized by the presence of extracellular amyloid deposits (composed mainly of β-amyloid, Aβ) and intraneuronal tangles (consisting largely of the cytoskeletal protein tau) in specific brain regions**, and **mutations in the APP gene, the presenilin 1 gene, the presenilin 2 gene** were known to associate with Alzheimer's disease as taught at least by Duff et al. (WO 98/17782; IDS) and Mucke et al. (US 6,455,757). The term "Alzheimer's disease gene" is defined as **a homolog of a human gene that has genetic variants associated with an increased risk of Alzheimer's disease or that encodes a gene product associated with Alzheimer's disease** (page 14, lines 13-17). Therefore, apart from the known mutations for the APP gene, presenilin 1 gene and presenilin 2 gene, what are **the essential structural features and/or elements for other genetic variants (including homologs and/or orthologs) associated with Alzheimer's disease derived from any organism** (e.g., any invertebrate as well as any vertebrate)? For example, what are the specific mutation features for genes such as har38, α-adaptin, garnet, *mastermind*, *big brain*, as well as their homologs and/or orthologs that are associated directly with the Alzheimer's disease?

Furthermore, as the breadth of the claims encompasses the use of transgenic organisms as fist and second parent strains to be used in the screening method for a

therapeutic agent for treating Alzheimer's disease, it should also be noted that the art of transgenic was and continues to be highly unpredictable with respect to the attainment of a desired phenotype, **including a phenotype associated with Alzheimer's disease**, as evidenced at least by the teachings of Hammer et al. (J. Anim. Sci. 63:269-278, 1986; Cited previously); Ebert et al. (Molecular Endocrinology 2:277-283, 1988; Cited previously); Strojek and Wagner (Genetic Engineering: Principles and Methods, vol. 10, pages 221-246, 1988; Cited previously); Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992; Cited previously); Mullins et al. (J. Clin. Invest. 98:S37-S40, 1996; Cited previously); and Wall, R.J. (Theriogenology 45:57-68, 1996; Cited previously).

The claimed invention as a whole is not adequately described **if the claims require essential or critical elements which are not adequately described in the specification** and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). A skilled artisan cannot envision the detailed structure for a representative number of species for a broad genus of a first parent strain (any invertebrate as well as any vertebrate) and/or a second parent strain (any invertebrate as well as any vertebrate) and/or **a test progeny having an altered phenotype relative to at least one sibling control and is relevant to the Alzheimer's disease**,

such that **the modification of the altered phenotype in the test progeny to a wild type phenotype by an agent would indicate that the agent is a therapeutic agent for treating Alzheimer's disease** in the method as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Response to Arguments***

Applicant's arguments related to the above rejection in the Amendment filed on 11/02/06 (pages 8-9) have been fully considered, but they are respectfully not found to be persuasive.

Applicants argue basically that the specification provides parental strains other than *Appl*$^{d}$ for practicing the claimed invention because the specification discloses numerous Alzheimer's disease genes, including genes interacting directly or indirectly with *Appl* such as *Notch, mastermind, big brain, har38*, CreB activator, CrebB inhibitor, alpha-adaptin, garnet, as well as a dozen specific differentially expressed genes in

Tables 4-6. Therefore, one skilled in the art would have appreciated that Applicants were in possession of parental strains other than the *Drosophila Appl*$^{d}$ in sufficient numbers to show possession of the genus of parent strains that carry a mutation in an Alzheimer's disease gene.

The issue is not simply that the instant specification discloses numerous alleged Alzheimer's disease genes, including genes interacting directly or indirectly with *Appl* such as *Notch, mastermind, big brain, har38,* CreB activator, CrebB inhibitor, alpha-adaptin, garnet, as well as a dozen specific differentially expressed genes in Tables 4-6. Firstly, there is no evidence of record or in the prior art at the effective filing date of the present application indicating that any mutation of the above genes, including their homologs and/or orthologs is associated with the Alzheimer's disease, specifically capable of producing the pathological features of the Alzheimer's disease characterized **by the presence of extracellular amyloid deposits (composed mainly of β-amyloid, Aβ) and intraneuronal tangles (consisting largely of the cytoskeletal protein tau) in specific brain regions.** Secondly, what are the specific structural characteristics/elements possessed by these mutant genes? For example, which specific mutation? Moreover, what **are the specific structural characteristics or phenotypes possessed by any organism containing any of these alleged mutant Alzheimer's disease genes**? Thirdly, as already noted in the above rejection the instant specification fails to teach and/or describe fully the **essential characteristics and/or elements** possessed by a representative number of species for a broad genus of a first parent strain (any invertebrate as well as any vertebrate) and/or a second

parent strain (any invertebrate as well as any vertebrate) and/or **a test progeny having an altered phenotype relative to at least one sibling control and is relevant to the Alzheimer's disease**, such that **the modification of the altered phenotype in the test progeny to a wild type phenotype by an agent would indicate that the agent is a therapeutic agent for treating Alzheimer's disease**. Fourthly, a phenotype of defective phototaxis exhibited by the *App*$^{d}$ *Drosophila* parent strain and/or the non-specific phenotype of either increased or decreased viability relative to sibling control observed for exemplified testing *Drosophila* progenies has nothing whatsoever with the hall-mark pathological features of the Alzheimer's disease.

Accordingly, claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, for the lack of Written Description for the reasons set forth above.

***Claim Rejections - 35 USC § 112***

Claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a therapeutic agent for treating Alzheimer's disease using progenies of art-recognized transgenic mouse models for Alzheimer's disease, does not reasonably provide enablement for other embodiments of a method for identified a therapeutic agent for treating Alzheimer's disease as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. ***This is a modified rejection.***

The specification teaches by exemplification showing a method of mapping genes acting in the same network as the *Drosophila* amyloid protein precursor-like gene (*Appl*) by crossing male *Drosophila* bearing a chromosome that lacks the *Appl* gene ($Appl^d$) with a series of *Drosophila* FM7 virgin females bearing individual deficiencies of the X chromosome "Df(1)s". Applicants further disclose that the $Appl^d$ *Drosophila* parent strain exhibits **a phenotype of defective phototaxis**, and that test progenies resulting from crossings of this $Appl^d$ *Drosophila* parent strain with a series of *Drosophila* females bearing individual deficiencies of the X chromosome display **a non-specific phenotype of either increased or decreased viability** with respect to a sibling control.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

***1. The breadth of the claims***

The claims are directed to a method of **identifying a therapeutic agent for treating Alzheimer's disease**, comprising the steps of: (a) performing matings between **any first parent strain from any transgenic or non-transgenic organism** (e.g., any invertebrate as well as any vertebrate, including any mammal) carrying **any mutation in any Alzheimer's disease gene** and **a second parent strain from any transgenic or non-transgenic organism containing any genetic variation**, whereby a test progeny is produced and **it has any altered phenotype relative to at least one sibling control**; (b) administering an agent to at least the first parent strain, the second parent strain or the test progeny; and (c) assaying the test progeny for a modification of

the altered phenotype that produces a phenotype with more similarity to a wild type phenotype; the same method with various limitations recited in the dependent claims.

***2. The state and the unpredictability of the prior art***

At about the effective filing date of the present application, the transgenic art was highly unpredictable with respect to transgene behavior *in vivo* and the attainment of any desired phenotype (for this instance a relevant phenotype associated with the Alzheimer's disease) as evidenced by the teachings of Hammer et al. (J. Anim. Sci. 63:269-278, 1986), Ebert et al. (Molecular Endocrinology 2:277-283, 1988), Strojek and Wagner (Genetic Engineering: Principles and Methods, vol. 10, pages 221-246, 1988), Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992), Mullins et al. (J. Clin. Invest. 98: S37-S40, 1996), and Wall, R.J. (Theriogenology 45:57-68, 1996).

Hammer et al. reported the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al. also reported a transgenic pig that did not develop an expected phenotype of growth during the rapid growth phase upon transfection with a Moloney murine leukemia virus rat somatotropin fusion gene (abstract, page 277). Mullins et al. stated "a given construct may react very differently from one species to another" (page S39, Summary). Wall further stated "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 62, first paragraph), and "[o]ur

lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph). Wall also noted that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a desired phenotype. Kappel et al. disclosed the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, col. 2, third full paragraph), while Strojek and Wagner pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because for example, the *cis* acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238 and 239).

The unpredictability of obtaining a desired phenotype exhibited by a transgenic animal is further supported by the teachings of Higgins et al. (Methods 10:384-391, 1996). With respect to genetically engineered animal models of Alzheimer's disease, Higgins et al stated "Much of the transgenic effort to model Alzheimer's disease has been frustrating, with a large body of disappointing results remaining unpublished. However, a few groups have described quite interesting and relevant transgenic phenotypes, and significant successes in the past year have been particularly encouraging and exciting" (page 384, col. 2, bottom of the full paragraph). Higgins et al further noted that the behavior of *Drosophila*, in which the β-APP homolog, *Appl*, was

deleted, **was essentially normal** (page 389, col. 2, bottom of first paragraph). Alzheimer's disease is a neurodegenerative disorder with a progressive dementia **characterized by the presence of extracellular amyloid deposits (composed mainly of β-amyloid, Aβ) and intraneuronal tangles (consisting largely of the cytoskeletal protein tau) in specific brain regions**, and **mutations in the APP gene, the presenilin 1 gene, the presenilin 2 gene** were known to associate with Alzheimer's disease at about the effective filing date of the present application as evidenced at least by the teachings of Duff et al. (WO 98/17782; IDS) and Mucke et al. (US 6,455,757).

***3. The amount of direction or guidance provided***

Apart from the teachings showing that the *Appl*$^{d}$ *Drosophila* parent strain exhibits **a phenotype of defective phototaxis**, and that test progenies resulting from crossings of this *Appl*$^{d}$ *Drosop hila* parent strain with a series of *Drosophila* females bearing individual deficiencies of the X chromosome display **a non-specific phenotype of either increased or decreased viability** with respect to a sibling control, the specification fails to provide sufficient guidance for a skilled artisan on how to generate a broad spectrum of a test progeny derived from any organism having an altered and relevant phenotype relative to a sibling control, such that a modulation of such a phenotype by an agent would indicate the agent as a therapeutic agent for treating Alzheimer's disease in the method as claimed. It is unclear how a phenotype of defective phototaxis exhibited by the *Appl*$^{d}$ *Drosophila* parent strain and/or the non-specific phenotype of either increased or decreased viability relative to sibling control

observed for exemplified testing *Drosophila* progenies has anything to do specifically to the hall-mark pathological features of the Alzheimer's disease. Moreover, Fossgreen et al. (PNAS 95:13703-13708, 1998) teaches the expression of full-length human APP forms (including both wild-type and Swedish APP mutant) in transgenic *Drosophila* results only in a blistered wing phenotype with the absence of βA4 production. This blistered wing phenotype has no correlation whatsoever with any pathological features associated with the Alzheimer's disease. Furthermore, there is no evidence of record or in the prior art at the effective filing date of the present application that any mutation in any gene such as har38, α-adaptin, garnet, *mastermind*, *big brain*, as well as their homologs and/or orthologs that are associated with the Alzheimer's disease in any organism, including *Drosophila*. Therefore, it would have required undue experimentation for a skilled artisan to screen for or identify a therapeutic agent for treating Alzheimer's disease in an organism that does not exhibit any relevant pathological hallmarks of the Alzheimer's disease.

Furthermore, given the highly unpredictability of a transgene behavior and/or transgene expression *in vivo* (variable among animal species and/or transgene constructs, and/or the presence or absence of essential *cis* acting elements and trans-acting factors among the different animal species) that results in the unpredictability for the attainment of a desired phenotype in any transgenic animal as discussed above, it would have required undue experimentation for a skilled artisan to generate test progenies derived from any organism having relevant altered phenotypes obtained by mating between a first parent strain carrying a mutation in an Alzheimer's disease gene

and a second parent strain containing a genetic variation for the screening of a therapeutic agent for treating Alzheimer's disease in the method as claimed.

Furthermore, with respect to the breadth of the instant claims, Applicants are directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the transgenic art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

***Response to Arguments***

Applicant's arguments related to the above rejection in the Amendment filed on 11/02/06 (pages 9-13) have been fully considered, but they are respectfully not found to be persuasive.

1. Applicants argue that the specification is enabled for the method as claimed because it teaches a variety of behavioral, morphological, and other physical

phenotype useful in the methods of the invention, including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability, as well as other useful phenotypes such as the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color or optomotor response of zebra fish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeasts.

It is noted that none of the above phenotypes has anything to do specifically to the well characterized pathological hallmarks of the Alzheimer's disease which are characterized by the presence of extracellular amyloid deposits (composed mainly of β-amyloid, Aβ) and intraneuronal tangles (consisting largely of the cytoskeletal protein tau) in specific brain regions.

2. With respect to references directed to transgenic techniques, Applicants argue that enablement of every single embodiment within the scope of the claims is not a prerequisite for the enablement of the claimed methods. Applicants further argue that while the methods of the invention are exemplified using the genetic system of *Drosophila*, any genetic system suitable for transmission genetics and convenient analysis of test and sibling control progeny (e.g., mice, zebrafish, nematodes, yeast) is useful for practicing the methods of the invention. At the time of filing, those skilled in the art had knowledge that human disease gene homologs had been identified in a variety of genetic systems and, given the broad teachings and guidance for the use and

applicability of the claimed methods with regard to species other than *Drosophila*, would have appreciated Applicants possessed the full scope of the claimed invention.

Please refer to the unpredictability of obtaining a desired phenotype exhibited by a transgenic animal, for this instance **the attainment of a relevant phenotype associated with the Alzheimer's disease**, as discussed in details above. With respect to genetically engineered animal models of Alzheimer's disease, Higgins et al stated "Much of the transgenic effort to model Alzheimer's disease has been frustrating, with a large body of disappointing results remaining unpublished. However, a few groups have described quite interesting and relevant transgenic phenotypes, and significant successes in the past year have been particularly encouraging and exciting" (page 384, col. 2, bottom of the full paragraph). Higgins et al further noted that the behavior of *Drosophila*, in which the β-APP homolog, *Appl*, was deleted, **was essentially normal** (page 389, col. 2, bottom of first paragraph). Therefore, apart from the enabled scope given it would have required undue experimentation for a skilled artisan to generate test progenies derived from any organism having relevant altered phenotypes obtained by mating between a first parent strain carrying a mutation in an Alzheimer's disease gene and a second parent strain containing a genetic variation for the screening of a therapeutic agent for treating Alzheimer's disease in the method as claimed.

3. With respect to the cited Fossgreen reference, Applicants argue that the presence of any altered phenotype in *Drosophila* can be related to Alzheimer's disease,

including the blistered wing phenotype displayed by transgenic *Drosophila* expressing human APP, given that the gene products are functionally equivalent and that flies are generally not subject to diagnosis with Alzheimer's disease or post-mortem autopsy to determine the presence of amyloid plaques. Applicants further argue that the Fossgreen reference supports the role of APP in cell adhesion and interaction with integrins, which Fossgreen reports to be associated with short-term memory in *Drosophila* and suggestive of a link with "memory mechanism".

The "blistered wing" phenotype in *Drosophila* has not been recognized in the art as a hallmark for the Alzheimer's disease, nor does any non-specific altered phenotype observed in *Drosophila*. The Fossgreen reference teaches clearly that the expression of full-length human APP forms (including both wild-type and Swedish APP mutant) in transgenic *Drosophila* results only in a blistered wing phenotype **with the absence of βA4 production**. In the absence of βA4 production, amyloid deposits or plaques can't be formed. There is also no evidence indicating these transgenic *Drosophila* exhibits memory loss similar in any shape or form as that of Alzheimer's disease, and that any suggestion made by Fossgreen is merely speculation.

Accordingly, claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In independent claim 22, it is unclear what is encompassed by the phrase "assaying the test progeny for the altered phenotype" in step (c). This is because which test progeny and/or which altered phenotype do Applicant refer to? The test progeny with an altered phenotype recite in step (a)? Additionally, what is the relevance for the embodiments of step (b) in administering an agent to the first parent strain or the second parent strain with step (c) for assaying the test progeny already has altered phenotype as recited in step (a)? Furthermore, the phrase "producing a phenotype with more similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype" is unclear. What exactly do Applicants mean? Clarification is requested because as written the metes and bounds of independent claim 22 and its dependent claims are not clearly determined.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-23, 25 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Mucke et al. (US 6,455,757). ***This is a new ground of rejection.***

Mucke et al already teaches a method for preparing a bigenic mouse expressing both bovine bioactive TGF-beta1 and human amyloid beta precursor protein (APP), wherein the transgenic mouse develops within about three months of age cerebrovascular amyloid deposits, and wherein, at about 12 months of age, the transgenic mouse has a significantly reduced number of neuritic amyloid plaques in the brain parenchyma, and an increase in cerebrovascular amyloid deposits, relative to a transgenic mouse that expresses only hAPP (see at least the abstract; col. 9, line 19 continues to line 20 of col. 10; and the claims). Mucke et al further teaches that the bigenic mouse can be prepared by crossing a singly transgenic APP mouse with a singly transgenic TGF-beta1 mouse (col. 12, lines 17-30; col. 17, lines 25-29). Mucke et al also discloses the use of the bigenic mouse to screen drugs or identify ligands or substrates that modulate the phenotype associated with AD by analyzing neuritic plaques and neurofibrillary tangles in the brain (col. 17, line 30 continues to line 57 of col. 19). Since the bigenic mouse has a significantly reduced number of neuritic amyloid plaques in the brain parenchyma over time relative to a transgenic mouse that expresses only hAPP, the bigenic mouse should have an increased life span (within a broad scope of increased viability) relative to littermate age-matched single transgenic mouse expressing only hAPP. With respect to claim 25, the examiner interprets the term "Psn" as presenilin.

Accordingly, the teachings of Mucke et al meet every limitation of the instant claims as written.

Claims 22-23, 25 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Duff et al. (WO 98/17782; IDS). ***This is a new ground of rejection.***

Duff et al already discloses at least a method for preparing a transgenic mouse with enhanced, accelerated pathology for Alzheimer's disease, comprising producing an F1 generation by crossing a first and a second mouse transgenic parent each carrying a different expressible transgene for different aspects of the same desired phenotype associated with AD pathology, including a mutant presenilin transgene (PS1 M140L mutation) and a transgene for a mutant amyloid precursor protein (APP695 isoform containing a K670N, M671L mutation) (See at least the abstract and Summary of the Invention on pages 7-8). Duff et al found that the double transgenic mice had accelerated formation of deposits containing Aβ, where no Aβ deposits was found in littermate age-matched single transgenic mice and non-transgenic mice littermates (page 14, first full paragraph). Duff et al further teaches that the offspring of the F1 generation with the above modulated phenotype are utilized in animal models as for example testing of treatment modalities in a disease model (page 10, lines 19-22), as well as testing the efficacy of agents proposed to interact with select aspects of the AD phenotype (page 22, first paragraph). Since these double transgenic mice have accelerated formation of Aβ deposits, a hallmark for the Alzheimer's disease, they should have a decreased life span (within a broad scope of decreased viability) relative

to littermate age-matched single transgenic mice and non-transgenic mice littermates that do not have Aβ deposits. With respect to claim 25, the examiner interprets the term "Psn" as presenilin.

Accordingly, the teachings of Duff et al meet every limitation of the instant claims as written.

***Conclusion***

***No claims are allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

**Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.**

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D.
PRIMARY EXAMINER